D.M. KISCH INCORPORATED, Johannesburg

FORM P.1

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

APPLICATION FOR A PATENT AND ACKNOWLEDGEMENT OF RECEIPT
(Section 30(1) — Regulation 22)
The grant of a patent is hereby requested by the undermentioned applicant on the basis of the present application filed in duplicate.

PATENT APPLICATION NO.	APPLICANT'S OR AGENT'S REFERENCE
21 01 842571	P/84/40849

FULL NAME(S) OF APPLICANT(S)

71 MERCK & CO., INC. a corporation of New Jersey U.S.A.

ADDRESS(ES) OF APPLICANT(S)

72 126 East Lincoln Avenue
Rahway, New Jersey 07065, United States of America

TITLE OF INVENTION

54 NOVEL SYNERGISTIC ANTIPARASITIC COMBINATIONS

X	THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2		
	THIS APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO.	21	01
	THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND BASED ON APPLICATION NO.	21	01

THIS APPLICATION IS ACCOMPANIED BY:

X	1	A single copy of a provisional or two copies of a complete specification of 16 pages.
	2	Drawings of sheets.
X	3	Publication particulars and abstract (Form P.8 in duplicate).
	4	A copy of Figure of the drawings (if any) for the abstract.
X	5	An assignment of invention.
X	6	Certified priority document(s) (State number). US Nos. 483,043; 483,044; 483,046; 483,047; 483,048; 483,049; 493,558
	7	Translation of the priority document(s).
	8	An assignment of priority rights.
	9	A copy of the Form P.2 and the specification of S.A. Patent Application No. 21 01
X	10	A declaration and power of attorney on Form P.3
	11	Request for ante-dating of Form P.4.
	12	Request for classification on Form P.9.
X	13	Request for delay acceptance on form P.4

DATED THIS 5th DAY OF April 19 84

Patent Attorney / Agent for the applicant(s)

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EN OCTROOIREGISTER

FORM P.7

D.M. KISCH INCORPORATED

Patent Attorneys & Trademark Agents
Attorneys & Notaries

REPUBLIC OF SOUTH AFRICA

THE PATENTS ACT, 1978.

COMPLETE SPECIFICATION

(Section 30 (1) — Regulation 28)

PATENT APPLICATION NO.	
21 01	84/2571

LODGING DATE	
22	[illegible] -04- 1984

INTERNATIONAL CLASSIFICATION	
51	C07D and C07H

FULL NAME(S) OF APPLICANT (S)	
71	MERCK & CO., INC.

FULL NAME(S) OF INVENTOR(S)	
72	WILLIAM C. CAMPBELL MICHAEL H. FISHER

TITLE OF INVENTION	
54	NOVEL SYNERGISTIC ANTIPARASITIC COMBINATIONS

TITLE OF THE INVENTION

NOVEL SYNERGISTIC ANTIPARASITIC COMBINATIONS

BACKGROUND OF THE INVENTION

Avermectin compounds are a series of natural products isolated from the fermentation broth of a strain of Streptomyces avermitilis. The series consists of eight compounds, four major and four minor. The compounds are disclosed in U.S. Patent 4,310,519. Certain derivatives of such compounds are also disclosed, such as the 22,23-dihydro derivatives described in U.S. Patent 4,199,569. The 13-deoxy derivatives of avermectin compounds are disclosed in U.S. Patents 4,171,314 and 4,173,571. In addition, the 4"-phosphate derivatives of the avermectin compounds with a 13-O-disaccharide group present, are included in the instant combination. Such compounds are disclosed in copending U.S. Patent Application Serial No. 461,843.

The synergistic combinations includes combining compounds such as niclosamide, which is disclosed in The Merck Index, Ninth Edition, Abstract

6332; rafoxanide, which is disclosed in The Merck Index, Ninth Edition, Abstract 7915; coumaphos, which is disclosed in The Merck Index, Ninth Edition, Abstract 2543; carbaryl, which is disclosed in The Merck Index, Ninth Edition, Abstract 1790; praziquantel, which is disclosed in J. Seubert, R. Pohlke and F. Loebich, Experienta 33, 1036 (1977); tetramisole and levamisole, which are disclosed in The Merck Index, Ninth Edition, Abstract 8949; and piperazine, which is disclosed in The Merck Index, Ninth Edition, Abstract 7254.

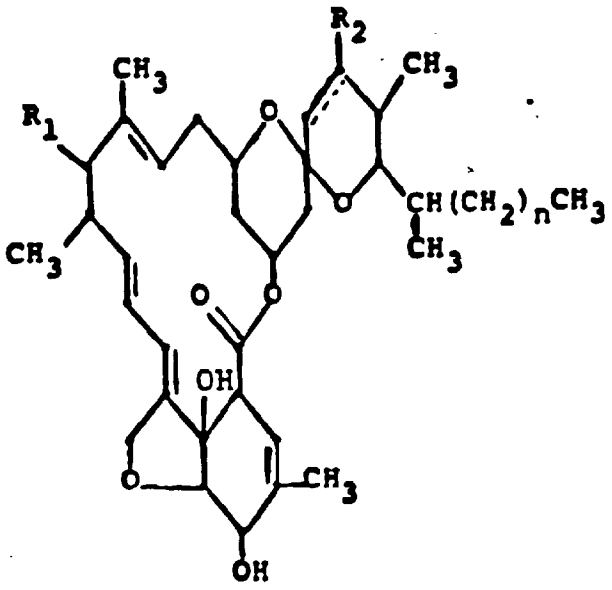
SUMMARY OF THE INVENTION

The instant disclosure describes certain synergistic combinations of avermectin compounds and niclosamide, rafoxanide, coumaphos, carbaryl, praziquantel, tetramisole, levamisole or piperazine. Thus, it is an object of this invention to describe such synergistic combinations. It is a further object to describe the individual components of such synergistic combinations and the relative proportion of each component in the combination. A still further object of this invention is to describe the antiparasitic and anthelmentic effects of such combinations. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The instant invention consists of a combination of avermectin compounds and niclosamide, rafoxanide, coumaphos, carbaryl, praziquantel, tetramisole, levamisole or piperazine combining compounds which have a synergistic effect when administered to animals for the treatment of

parasitic diseases. The avermectin compounds of this invention have the following formula:



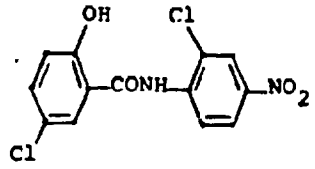
wherein n is 0 or 1;

R_1 is hydrogen, α-L-oleandrosyl-α-L-oleandrosyloxy and the 4"-phosphate derivative thereof;

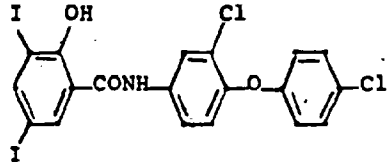
R_2 is hydrogen; and

the broken line indicates a single or a double bond; however, R_2 is present only when the broken line indicates a single bond.

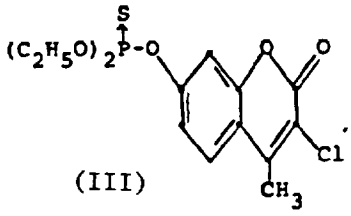
The combining compounds, niclosamide (I), rafoxanide (II), coumaphos (III), carbaryl (IV), praziquantel (V), tetramisole and levamisole (VI) and piperazine(VII) which constitute the second part of the instant synergistic combinations have the following formulae:



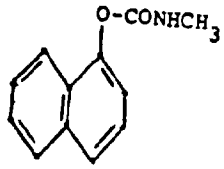
(I)



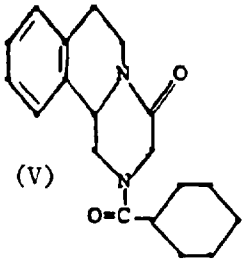
(II)



(III)



(IV)



(V)

(VI)

and

(VII)

respectively.

In addition, pharmaceutically acceptable salts of the combining compounds may be employed, such as the hydrochloride, citrate, adipate and the like salts.

When used as antiparasitic agents the avermectin compounds are administered at dosage rates of from 0.001 to 10 mg of the active compound per kg of weight of the host animal. When used as antiparasitic agents the combining compound is administered at dosage rates of from 10 to 800 mg of the active compound per kg of weight of the host animal.

The synergistic effects of the combination of the avermectin compounds with a combining compound are observed in providing for a reduced dosage of one or both of the components. Thus, a lessened quantity of the antiparasitic compounds is administered than normally would be required which results in a lessening of possible side effects and a lessening in the development of resistance. In addition, there is observed the synergistic expansion of the spectrum of parasitic infections which may be successfully combatted than would be expected for a consideration of the spectra of activity of the individual components. Thus, the possibility of eliminating parasitic infections against which the individual components are ineffective or only partially effective is realized in the instant synergistic combination.

The parasitic infections against which the instant synergistic combination is particularly effective are species of the genera Dipylidium, Taenia, Echinococcus, Ancylostoma, Strongyloides, Haemonchus, Fasciola, Arthropes, Parasites, Cestodes, Cestode-Nematode, Toxocara Toxascaris, Heterakis, Parascaris, Ascaris, Neoascaris, Asgarida, and the like, as may be found in dogs, cats, sheep, cattle, horses, pigs and other animals.

In using the instant synergistic combination, the individual components are used in proportions which may extend to from 0.5 part of the avermectin compound to 50 parts of combining compound, to from 1 part of the avermectin compound to 5000 parts of combining compound.

The synergistic combination may be administered orally in unit dosage form such as a capsule, bolus or tablet, or as a liquid drench where used as an antiparasitic in mammals. The drench is normally a solution, suspension or dispersion of the active ingredients usually in water together with a suspending agent such as bentonite and a wetting agent or like excipient. Generally, the drenches also contain an antifoaming agent. Drench formulations generally contain from about 0.001 to 0.5% by weight of the active compounds. Preferred drench formulations may contain from 0.01 to 1% by weight. The capsules and boluses comprise the active ingredients admixed with a carrier vehicle such as starch, talc, magnesium stearate, or dicalcium phosphate.

Where it is desired to administer the synergistic combination in a dry, solid unit dosage form, capsules, boluses or tablets containing the desired amount of active compounds usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredients with suitable finely divided diluents, fillers, disintegrating agents and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the synergistic combination is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets which may then be added to the finished feed or optionally fed separately. Alternatively, the antiparasitic combination of our invention may be administered to animals parenterally, for example, by intraruminal, intramuscular, intratracheal, or subcutaneous injection in which event the active ingredient is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral vehicles such as organic preparations using solketal, glycerol, formal and aqueous parenteral formulations are also used. The active

compounds are dissolved or suspended in the parenteral formulation for administrations; such formulations generally contain from 0.005 to 5% by weight of the active compound.

EXAMPLE I

Specific formulations containing avermectin compounds and a combining compound (niclosamide) which have synergistic antiparasitic effects are as follows:

A tablet containing 250 mg of niclosamide, and 0.5 mg of ivermectin is given orally to a dog weighing 5.0 kg body weight, and harboring species of the genera Dipylidium, Taenia, Echinococcus, Ancylostoma and Strongyloides. The treatment results in a high degree of efficacy against the said parasite species.

In addition, an oral drench, a controlled release bolus or a feed supplement may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.2 mg/kg and niclosamide at 50 or 100 mg/kg.

EXAMPLE II

Specific formulations containing avermectin compounds and a combining compound (rafoxanide) which have synergistic antiparasitic effects are as follows:

A suspension is prepared containing 8.3 mg rafoxanide per ml and 0.3 mg ivermectin per ml, and suitable excipients to provide a ready-to-use, free-flowing suspension. A volume of 6 ml of this suspension is given orally by conventional dosing syringe to a sheep weighing 20 kg body weight and

harboring parasites of the genera Fasciola, Haemonchus, Trichostrongylus, Dermacentor and Psoroptes. The treatment results in a high degree of efficacy against the said parasites.

In addition an oral drench, a controlled release bolus or a feed supplement may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.2 mg/kg and rafoxanide at 2.5 mg/kg.

A solution or suspension or other formulation suitable for parenteral administration may be prepared containing the active ingredients in quantities sufficient to provide ivermectin at a dosage of 0.2 mg/kg and rafoxanide at 2.5 mg/kg.

EXAMPLE III

Specific formulations containing avermectin compounds and a combining compound (coumaphos) which have synergistic antiparasitic effects are as follows:

A powder is prepared, consisting of talc containing coumaphos at a concentration of 0.01% w/v. A solution is prepared containing glycerol formal at 40% v/v, propylene glycol at 60% v/v and ivermectin at 1.0% w/v. The powder is dusted liberally onto the surface of a calf weighing 100 kg body weight and harboring parasites of the genera Ostertagia, Cooperia, Nematodirus, Damalinia, Hypoderma, Hyalomma and Chorioptes. On the same day the calf is injected subcutaneously with a solution consisting of glycerol formal at 40% v/v, propylene glycol 60% v/v and ivermectin at 1.0% w/v, the calf being given a volume of 1 ml of the solution. The treatment results in a high degree of efficacy against the said parasite species.

In addition, dips, sprays, "pour-on" solutions, or other formulations suitable for external application may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.001% weight/volume and coumaphos at 1.0% weight/volume.

Oral or parenteral formulations, may be prepared to deliver ivermectin at a dosage of 0.1 mg/kg once, or 0.01 mg/kg daily in conjunction with suitable topical formulations (dip, spray, "pour-on", etc.) containing coumaphos at 1.0% weight/volume.

Oral drench, tablet, controlled release bolus or feed supplements may be prepared containing the active ingredients in quantities sufficient to provide ivermectin at 0.1 mg/kg once or 0.01 mg/kg daily and coumaphos at 5.0 mg/kg once or 1.0 mg/kg daily.

EXAMPLE IV

Specific formulations containing avermectin compounds and a combining compound (carbaryl) which have synergistic antiparasitic effects are as follows:

A standard commercial spraying device is charged with water containing carbaryl at 1.0% w/v. Into this device is place a calf weighing 100 kg and harboring parasites of the genera Ostertagia, Nematodirus, Cooperia, Damalinia, Boophilus, Dermacentor and Psorergates. The calf is liberally sprayed with the spraying solution. On the same day the calf is injected subcutaneously with a solution consisting of glycerol formal at 40% v/v, propylene glycol 60% v/v and ivermectin at 1.0% w/v, the calf

being given a volume of 1 ml of the solution. The treatment results in a high degree of efficacy against the said parasite species.

In addition, dips, sprays, "pour-on" solutions or other preparations suitable for external application may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.001% weight/volume and carbaryl at 1.0% weight/volume.

In addition, an oral drench, a controlled release bolus, a feed supplement or a parenteral formulation may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.2 mg/kg or 0.01 mg/kg/day, in conjunction with a suitable topical preparation, such as a dip, spray, or "pour-on", containing carbaryl at 1.0% weight/volume.

EXAMPLE V

Specific formulations containing avermectin compounds and a combining compound (praziquantel) which have synergistic antiparasitic effects are as follows:

A tablet containing 25 mg of praziquantel, and 0.5 mg of ivermectin is given orally to a dog weighing 5.0 body weight, and harboring species of the genera Dipylidium, Taenia, Echinoccus, Ancylostoma and Strongyloides.

In addition, an oral drench, a controlled release bolus or a feed supplement may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.2 mg/kg and praziquantel at 5 or 50 mg/kg.

EXAMPLE VI

Specific formulations containing avermectin compounds and a combining compound (tetramisole or levamisole) which have synergistic antiparasitic effects are as follows:

A bacteriologically sterile solution is prepared, consisting of glycerol formal (40% v/v) and propylene glycol (60% v/v) and containing 25 mg levamisole per ml and 1 mg ivermectin per ml. The solution is injected subcutaneously into calves, each calf weighing 60 kg and harboring parasites of the genera Ostertagia, Dictyocaulus, Cooperia and Nematodirus. The treatment results in a high degree of efficacy against the said parasite species.

In addition, an oral drench, a controlled release bolus or a feed supplement may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.1 mg/kg and levamisole at 2.5 mg/kg.

A solution or suspension or other formulation suitable for parenteral administration may be prepared containing the active ingredients in quantities sufficient to provide ivermectin at a dosage of 0.1 mg/kg and levamisole at 2.5 mg/kg.

EXAMPLE VII

Specific formulations containing avermectin compounds and combining compounds (piperazine) which have synergistic antiparasitic effects are as follows:

A tablet containing 250 mg of the adipate salt of piperazine, and 0.5 mg of ivermectin, and suitable excipients, is given to a dog weighing 5.0 kg body weight, and harboring parasitic infections,

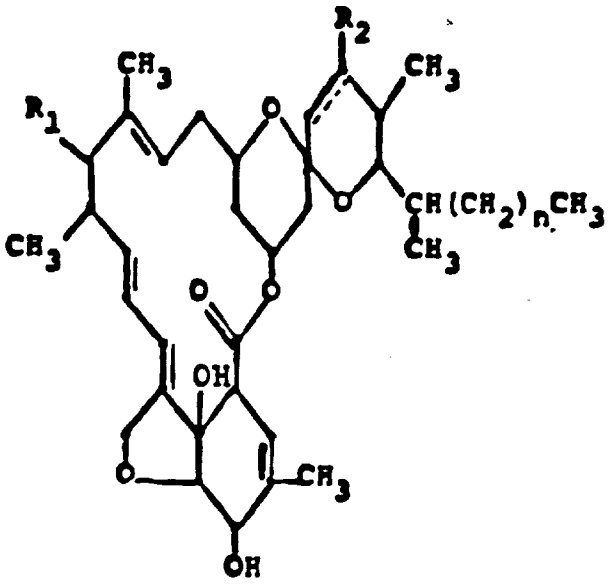
including species of the genera Toxocara, Toxascaris, Ancylostoma and Trichuris. The treatment results in a high degree of efficacy against the said parasites.

In addition, an oral drench, a controlled release bolus or a feed supplement may be prepared containing the active ingredients in quantities sufficient to deliver ivermectin at a dosage of 0.2 mg/kg and piperazine at 50 or 100 mg/kg.

84/2571

~~WHAT IS CLAIMED IS:~~

1. An antiparasitic synergistic combination of an avermectin compound having the formula:



wherein n is 0 or 1;

R_1 is hydrogen, α-L-oleandrosyl-α-L-oleandrosyloxy and the 4"-phosphate derivative thereof;

R_2 is hydrogen; and

the broken line indicates a single or a double bond; however, R_2 is present only when the broken line indicates a single bond; and a combining compound selected from the group consisting of niclosamide, rafoxanide, coumaphos, carbaryl, praziquantel, tetramisole, levamisole and piperazine.